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was true, as noted above, for the adverse events anaphylaxis and erythema multiforme or other rash. In the case of hemolytic anemia, a single striking case report was sufficient to suggest biologic relevance (see Chapter 6).

Historical Comparisons

Another aspect of case reports and case series that bears on the use of such evidence is their lack of external comparative observations. Accordingly, the measures of association described earlier in this chapter that provide evidence on the question of causation in general and, if affirmative, the extent of such causation are not attainable from these reports. In unusual circumstances, a case series may reflect the ascertainment of all cases from a defined population over a given period of time. It may therefore be possible to estimate rates of events for that population, and if such information is available for two distinct periods or over a very extended interval, historical comparisons or trends might be constructed. Such opportunities were not found, however, in the material available concerning pertussis or rubella vaccine and adverse events. Were it available, evidence of this kind would be applicable to the question of how much vaccine exposure might contribute to the occurrence of the event in the population.

Causation of the Individual Case

Case reports and case series data also bear on the question of causation of an individual case, for example, whether a given adverse event is an allergic response to pertussis vaccine. Individual cases of the adverse event could be examined to determine whether the event occurred in a clear sequence following each pertussis immunization in the series. An increasing severity of the event with increasing dose number would tend to support a causal interpretation. If the event tended to diminish in severity or was absent for later doses in the series, this evidence would tend to detract from a causal interpretation.

Although the temporal relation between the exposure and the event can at times seem to provide compelling evidence toward a causal interpretation, the possibility of simple coincidence, in light of the known background occurrence of most of the events under consideration, adds to the importance of careful evaluation of alternative explanations. Rarely, on the basis of case information alone, can alternative explanations be excluded.

Monitoring System for Adverse Events Following Immunization

Because of its prominence among sources of case reports, special note should be made of the CDC's Monitoring System for Adverse Events Fol-

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Three of these considerations (strength of association, dose-response relation, and temporally correct association) can be applied to the findings of single studies and can therefore be regarded, in part, as measures of internal validity. Any of these considerations can be satisfied in some, but not necessarily in all, studies testing a particular causal hypothesis. The other three considerations (consistency of association, specificity of association, and biologic plausibility) are not necessarily study specific and depend to varying degrees on prior knowledge.

Strength of Association Strength of association is usually expressed in epidemiologic studies as the magnitude of the measure of effect, for example, relative risk or odds ratio. Generally, the larger the relative risk, the greater the likelihood that the vaccine-event association is causal or, in other words, the less likely it is due to undetected error, bias, or confounding. Measures of statistical significance such as *p* values are not indicators of the strength of association.

Dose-Response Relation The existence of a dose-response relation—that is, an increased strength of association with increased exposures or other appropriate relation—strengthens an inference that an association is causal.

Temporally Correct Association If an observed association is causal, exposure must precede the event by at least the duration of disease induction. The committee, in addition, considered whether the adverse event occurred within a time interval following vaccination that was consistent with current understanding of its natural history. The committee interpreted the lack of an appropriate time sequence as strong evidence against causation, but recognized that insufficient knowledge about the natural history and pathogenesis of many of the adverse events under review limited the utility of this consideration.

Consistency of Association Consistency of association requires that an association be found regularly in a variety of studies, for example, in more than one study population and with different study methods. The committee considered findings consistent across different categories of studies as being supportive of a causal interpretation of the evidence.

Specificity of Association Specificity of association is the degree to which a given exposure predicts the frequency or magnitude of a particular outcome; if the association of the exposure and the event is unique to both, a causal interpretation seems more strongly justified than when the association is nonspecific to both the exposure and the event. The committee